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Clinical features of sarcoidosis associated pulmonary hypertension: Results of a multi-national registry

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ABSTRACT

Background: Pulmonary hypertension (PH) is a significant cause of morbidity and mortality in sarcoidosis. We established a multi-national registry of sarcoidosis associated PH (SAPH) patients.
Methods: Sarcoidosis patients with PH confirmed by right heart catheterization (RHC) were studied. Patients with pulmonary artery wedge pressure (PAWP) of 15 mmHg or less and a mean pulmonary artery pressure (mPAP) ≥ 25 Hg were subsequently analyzed. Data collected included hemodynamics, forced vital capacity (FVC), diffusion capacity of carbon monoxide (DL_{CO}), chest x-ray, and 6-min walk distance (6MWD).
Results: A total of 176 patients were analyzed. This included 84 (48%) cases identified within a year of entry into the registry and 94 (53%) with moderate to severe PH. There was a significant correlation between DL_{CO} percent predicted (% pred) andmPAP (Rho = −0.228, p = 0.0068) and pulmonary vascular resistance (PVR) (Rho = −0.362, p < 0.0001). PVR was significantly higher in stage 4 disease than in stage 0 or 1 disease (p < 0.05 for both comparisons). About two-thirds of the SAPH patients came from the United States (US). There was a significant difference in the rate of treatment between US (67.5%) versus non-US (86%) (Chi Square 11.26, p = 0.0008) sites.
Conclusions: The clinical features of SAPH were similar across multiple centers in the US, Europe, and the Middle East. The severity of SAPH was related to reduced DLCO. There were treatment differences between the US and non-US centers.

1. Introduction

Sarcoidosis associated pulmonary hypertension (SAPH) is associated with significant morbidity and an increased mortality [1–4]. The incidence of SAPH in a general sarcoidosis clinic varies between 5 and 20% [5–7]. The lower rates have been reported in general sarcoidosis clinics [5], while higher rates have been reported from tertiary referral clinics [6]. Over half of sarcoidosis patients with persistent dyspnea or listed for lung transplant have SAPH [1,8,9]. Despite increased recognition of SAPH over the past decade, there are still significant gaps in knowledge about this condition and there are no direct comparisons between the features or treatment of SAPH in various parts of the

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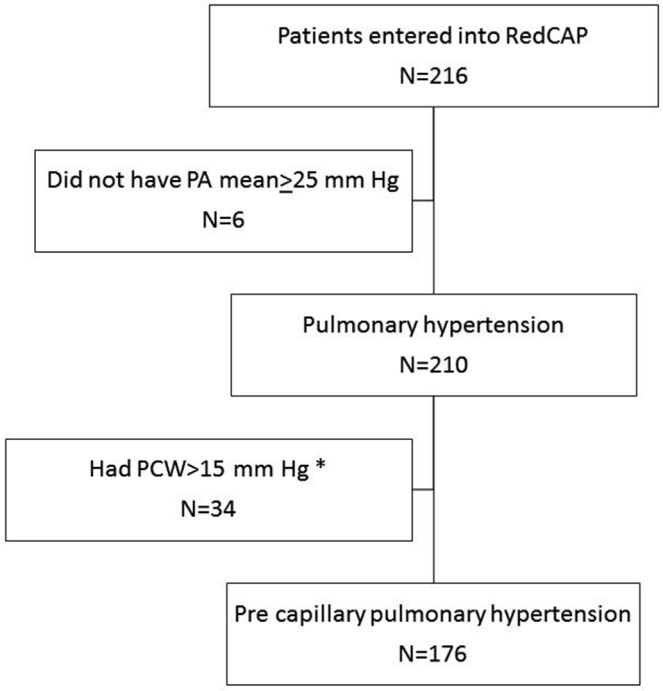

Fig. 1. Flow sheet of 216 patients in the sarcoidosis associated pulmonary arterial hypertension registry. Based on right heart catheterization measurements, 176 patients were identified with a pulmonary artery mean (mPAP) ≥ 25 mm Hg and a pulmonary capillary wedge (PAWP) of 15 mm Hg or less.

Table 1
Features of 176 patients with SAPH.

	N	SAPH
Number		176
Age		58 (34,81)[a]
Female:Male		125:51 (71%:19%)[b]
White/Black/Asian/Middle Eastern		57:96:5:19 (32%:55%:3%:11%)
RA, mm Hg	165	5 (0,21)[a]
sPAP, mm Hg	176	55 (35, 109)[a]
dPAP, mm Hg	175	22 (7, 65)[a]
mPAP, mm Hg	176	35 (25, 62)[a]
PAWP, mm Hg	176	10 (1,15)[a]
Cardiac Output	160	5.3 (2, 10.3)[a]
Cardiac Index	130	2.82 (1.2, 5.04)[a]
PVR	160	5.49 (1.85, 20.49)[a]
FVC % predicted	168	60 (19, 132)[a]
FEV_1% predicted	169	54 (22, 119)[a]
FEV_1/FVC %	167	74 (21, 98)[a]
DLCO % predicted	139	37 (13, 94)[a]
Chest X-ray Scadding stage		
0	7	7
1	4	4
2	12	12
3	23	23
4	89	89
Six-minute walk test results [a]		
Distance walked (m)	142	305 (11,610)[a]
End of walk Borg	142	4 (0,10)[a]
End of walk oxygen saturation (%)	142	90 (47, 100)[a]
Change in saturation during walk	142	−5 (−50, 10)[a]

RAP - right atrial pressure; sPAP- systolic pulmonary artery pressure, dPAP – diastolic pulmonary artery pressure, mPAP - mean pulmonary artery pressure; PAWP – pulmonary artery wedge pressure; PVR – pulmonary vascular resistance; FVC – forced vital capacity; FEV_1 – forced expiratory volume at 1 s; DL_{CO} – diffusion capacity for carbon monoxide.

[a] Median (Range).

[b] Number (percent).

world.

To gather more knowledge about the disease, we established an observational Registry for Sarcoidosis Associated Pulmonary Hypertension (ReSAPH) to prospectively collect data on patients with incident or prevalent SAPH. The registry was designed to collect information regarding the initial presentation and subsequent clinical course of SAPH patients from sarcoidosis centers across the world. Data collected included hemodynamic measures to assess severity of pulmonary hypertension, pulmonary function testing and chest imaging to characterize the underlying pulmonary involvement, and 6-min walk distance (6MWD). We also collected information on treatment for the pulmonary hypertension. We now report the analysis of the demographics, disease course, and management of the first 176 patients with pre-capillary SAPH and compare those results to pulmonary sarcoidosis patients without pulmonary hypertension. We also compared the clinical features of SAPH for United States (US) and non-US sites.

2. Materials and methods

Patients with a diagnosis of sarcoidosis based on the ATS/ERS/WASOG criteria and hemodynamic diagnosis of PH were enrolled in an eleven center observational registry [10]. The registry was initiated in October 2011. All patients were required to have at least one right heart catheterization (RHC) demonstrating a mean pulmonary artery pressure (mPAP) ≥ 25 mmHg. Incident cases were defined as the diagnosis of PH within one year of entry into the registry, whereas prevalent cases were diagnosed more than a year prior. Patients were recruited from individual clinic patients. There was no advertising or other efforts to recruit all SAPH patients within each geographic area of the individual clinic. The overall study was designed to recruit 200 patients with half of cases to be incident cases. This sample size was based on prior single center studies of SAPH patients. All information was recorded in a secure web-based electronic database (REDCap) [11]. Each investigator had obtained local institutional review board approval prior to entering any patient into the database. The study is registered at ClinTrials.gov at number NCT01467791. The authors used the STROBE (Strengthening The Reporting of Observational Studies in Epidemiology) checklist in preparing this report.

For each patient, the first RHC identifying PH was recorded. Values recorded included the mean right atrial (RA) pressure, systolic, diastolic, and mPAP, the pulmonary artery wedge pressure (PAWP), cardiac output (CO) by thermodilution, and cardiac index (CI). Pulmonary vascular resistance (PVR) was calculated and reported in Wood units.

At time of entry into the study, all patients underwent a history and focused physical examinations. Age, gender, self-declared race, organ involvement using standard criteria [12,13], duration of sarcoidosis and SAPH were recorded. Pulmonary function studies data obtained included forced vital capacity (FVC), forced expiratory volume in 1 s (FEV_1), the ratio of FEV_1 to FVC, (FEV_1/FVC) and diffusion capacity of carbon monoxide (DL_{CO}) with % predicted values using the local laboratory formulas correcting for race and hemoglobin. PH-specific therapy was recorded. When available, the most recent chest x-ray at the time of entry into the study was reviewed and staged using Scadding criteria [14].

For the US sites and one site in Europe (Rotterdam), additional information was obtained on all patients enrolled. Information collected included 6MWD using a standard protocol [15,16], oxygen saturation and Borg score [15] initially and at the end of walking, as well as the use and rate of supplemental oxygen during the test.

2.1. Statistics

Correlations between variables were calculated using Spearman rank correlation using MedCalc Statistical Software version 14.8.1 (MedCalc Software bvba, Ostend, Belgium; http://www.medcalc.org; 2014). Kruskal Wallis testing was performed to analyze for variance

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